MEMORANDUM August 22, 2008

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SUBJECT: Review of Acute Oral Toxicity, Acute Dermal Toxicity, Primary Dermal Irritation, Primary Eye Irritation and Twenty Eight-Day Oral Toxicity Studies with Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)- (P08-508) or Propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1) (P08-509), a Two-Week Inhalation Toxicity Study [redacted]

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[redacted]

I. CONCLUSIONS

The studies reviewed below adequately meet TSCA requirements for acute oral toxicity, acute dermal toxicity, dermal irritation, and eye irritation with P08-508 or P08-509. The acute oral toxicity studies with P08-508 or P08-509 indicate low acute oral toxicity. The acute dermal toxicity study with P08-509 indicates low acute dermal toxicity. High concern for eye irritation with [redacted] is concluded. Low concern for dermal irritation with P08-509 is supported. An acute dermal toxicity study with [redacted] indicating skin irritation was not confirmed by other studies with skin treatment with [redacted] which showed low or no skin irritation. An *in vitro* test in which P08-509 was reported as corrosive is inconclusive.

[redacted]

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A no-observable-adverse-effect level (NOAEL) was not established in 7-day oral toxicity studies with P08-508 or P08-509 in rats or mice at dose levels as low as 30 mg/kg/day based mainly on signs of liver toxicity.

In inhalation toxicity studies with 2 weeks of exposure to transformation byproducts, a NOAEL of 175,000 ppm was apparent with 1 substance and a NOAEL was not set with the other substance. In the SAT report on P08-508 and P08-509, these byproducts are noted as poor analogs.

Studies reviewed below adequately meet TSCA requirements for acute oral toxicity and 28-day oral toxicity testing with [redacted]. The acute oral LD50 is consistent with a low degree of toxicity. A no-observable-adverse-effect level (NOAEL) of 5 mg/kg/day in the 28-day oral toxicity study based on signs of kidney and liver toxicity at higher dose levels is concluded. Effects on blood were not determined in this study.

Application of the NOAEL in the study with [redacted] to P08-508 and P08-509 is not recommended, considering 30 mg/kg/day was not a NOAEL in the studies with P08-508 and P08-509 with only 7 days of treatment is not much higher than the 5 mg/kg/day NOAEL in the study with [redacted] with 28 days of treatment.

In the submission, proposed testing with P08-509 includes an inhalation LC_{50} study with histopathology in rats, a single dose pharmacokinetic study in mice, 28-day oral toxicity studies in rats and mice, an *in vitro* mouse lymphoma assay, 90-day oral toxicity studies in mice or rats, developmental toxicity studies in mice or rats, a 2-generation reproductive toxicity study in rats, a combined chronic toxicity/carcinogenicity study in rats or mice, metabolism studies in rats, and a plasma clearance study in primates. Mice or rats will be chosen based on 28-day study and metabolism study results.

II. BASIS FOR CONCLUSIONS

The PMN test substance, propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)- (P08-508) (CAS No. 13252-13-6), is a [redacted] with a molecular weight of 330, water solubility of 0.043 g/L, and vapor pressure of [redacted]. In the study reports, P08-508 is described as [redacted]

The PMN test substance, propanoic acid, 2,3,3,3-tetrafluoro-2-(1,1,2,2,3,3,3-heptafluoropropoxy)-, ammonium salt (1:1) (P08-509) (CAS No. 62037-80-3), is a [redacted] with a molecular weight of 347, water solubility described as dispersible, and vapor pressure of [redacted] (SAT Report). In the study reports, P08-509 is described as [redacted] (CAS No. 62037-80-3), a [redacted]

[redacted] or as [redacted]

P08-508 is expected to be absorbed by all routes. Expected absorption of P08-509 is good by lung and gastrointestinal tract and poor by skin (SAT Report).

a. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 425. One female Crl:CD (SD) rat per dose group were given neat test substance by gavage at a dose of 175 or 550 mg/kg, and 3 female Crl:CD (SD) rats per group were given neat test substance by gavage at a dose of 1,750 or 5,000 mg/kg. Animals were observed for survival, clinical signs, body weight, and gross pathology through sacrifice on study day 14.

No deaths occurred in the 175, 550, or 1,750 mg/kg groups. All females given 5,000 mg/kg died. by 2 days after dosing.

The reported acute oral LD_{50} was above 3,129 mg/kg.

Clinical signs in all rats included hair loss, high posture, stained and wet fur, clear ocular discharge, prostrate posture, partially closed eyes, and/or salivation. After test day 2, only hair loss was observed as a clinical sign.

Survivor body weight was normal.

Gross pathology in decedents was described as discoloration in lungs and mandible lymph nodes. Gross pathology in survivors was unremarkable.

The acute oral LD_{50} supports low acute oral toxicity in this study.

b. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 401; however, the report is sketchy. What appears to be 1 male Crl-CD BR rat per dose group was given aqueous test substance solution by gavage at one of a wide range of doses from 670 to 11,000 mg/kg. Animals were observed for survival, clinical signs, and body weight through sacrifice on day 14 post-treatment.

No deaths occurred with doses at and below 3,400 mg/kg . All males given higher doses died.

The acute oral LD_{50} was above 3,,400 mg/kg. An approximate lethal dose (ALD) of 7,500 mg/kg/was reported.

Clinical signs in surviving rats included stained fur and initial weight loss. Lethargy and low posture were observed in decedents.

The acute oral LD_{50} above 5,000 mg/kg supports low acute oral toxicity in this study. Use of only 1 rat per dose group was a weakness countered by use of numerous doses and low acute oral toxicity.

c. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 401; however, the report is sketchy. What appears to be 1 male Chr-CD rat per dose group was given aqueous test substance solution by gavage at one of a wide range of doses from 1.5 to 17,000 mg/kg. Animals were observed for survival, clinical signs, body weight, liver weight, liver histopathology, and presumably gross pathology through sacrifice on day 14 post-treatment.

No deaths occurred with doses at and below 5,000 mg/kg . All males given higher doses died. by 3.25 hours after dosing.

The acute oral LD_{50} was above 5,000 mg/kg. An ALD of 7,500 mg/kg was reported.

Clinical signs in surviving rats included discomfort, increased water intake, inactivity, polyuria, and initial weight loss in animals given 2,250, 3,400, or 5,000 mg/kg (increased liver weight and liver histopathology as enlarged hepatocytes and pronounced cell membranes were noted in these groups). Gasping and tonic convulsions were observed in decedents.

Slight to moderate degeneration in pancreas was stated, which would likely have been observed in histopathology. Because histopathology of 2 organs was reported, it is presumed that animals were examined for gross pathology and possibly histopathology of other organs with no treatment-related changes evident.

The acute oral LD_{50} above 5,000 mg/kg supports low acute oral toxicity in this study. Use

of apparently only 1 rat per dose group was a weakness countered by use of numerous doses and low acute oral toxicity. Liver and pancreas were shown as potential target organs for test agent toxicity in this study.

d. Acute Dermal Toxicity Study in with [redacted] in Rabbits

This study is consistent with OECD guideline 402. Onto intact skin shaved free of fur of each of 2 male New Zealand rabbits was applied 5,000 mg/kg of aqueous test material paste under semi-occlusive dressing. Exposure to test substance was 24 hours. Animals were observed for survival, clinical signs, body weight, and gross pathology through terminal sacrifice on study day 15. Irritation at test sites was scored by the Draize method. Gross pathology was not assessed.

All animals survived.

The acute dermal LD_{50} was above 5,000 mg/kg.

At test sites, erythema which reduced from severe/moderate to well-defined to very slight over time and epidermal scaling and sloughing were observed through study day 13 and were reported as cleared by study day 15. In 1 rabbit was observed necrosis attributed to test agent leaking outside the test site area and which sloughed study day 7 with alopecia evident until the end of the study. This conclusion on necrosis is uncertain to this reviewer since, if the test agent was capable of inducing this necrosis, then it seems that the test agent should have induced necrosis at the test sites. No edema at test sites was evident. This study was not a skin irritation test per guideline, i.e., OECD guideline 404; however, by Draize scoring (maximum score was 3), the test substance was moderately irritating in this study

Clinical signs and body weight were unremarkable.

Results of this study support low acute dermal toxicity by the test material.

e. Seven-Day Oral Toxicity Study with [redacted] in Rats

This study was designed to assess subacute toxicity and kinetics of the test substance given to rats for 7 days. Doses were corrected for test substance purity. In the subacute toxicity portion, 5 male and 5 female Crl:CD (SD) rats per group were given 0 (vehicle control), 30, 300, or 1,000 mg/kg/day of test substance in water by gavage daily for 7 days with terminal sacrifice on study day 8. Rats were 6 weeks old at the start of treatment. In the subacute toxicity portion, rats were evaluated for survival, clinical signs, body weight, hematology, clinical chemistry, gross pathology, histopathology, and organ weights.

All animals survived.

Clinical signs were unremarkable.

Body weight gain was slightly lower in males given 1,000 mg/kg/day.

In hematology, hemoglobin, red blood cell counts, and hematocrit were decreased in males given 300 or 1,000 mg/kg/day and in females given 1,000 mg/kg/day. In females given 1,000 mg/kg/day were increases in red blood cell distribution width, absolute reticulocyte counts, and absolute neutrophil counts.

In clinical chemistry, there were decreases in cholesterol, triglycerides, and globulin and increases in glucose in all treated groups of males, increases in biliary urea nitrogen and decreases in total protein and calcium in males given 300 or 1,000 mg/kg/day, increases in aspartate aminotransferase and alanine aminotransferase and decreases in sorbitol dehydrogenase, creatinine, and sodium in males given 1,000 mg/kg/day, increases in alanine aminotransferase and decreases in cholesterol in females given 300 or 1,000 mg/kg/day, and decreases in bilirubin, creatinine, total protein, and globulin in females given 1,000 mg/kg/day.

Absolute and relative (organ/body) liver weights were increased in all treated groups of males and in females given 1,000 mg/kg/day. Absolute and relative heart weights were decreased in males given 1,000 mg/kg/day. Absolute kidney weights were elevated in females given 1,000 mg/kg/day.

Gross pathology was unremarkable.

In histopathology, minimal to mild hepatocellular hypertrophy in liver was found in all treated groups of males and in females given 1,000 mg/kg/day.

A NOAEL is not established based on changes in clinical chemistry and organ weights indicative of liver effects in all groups of treated male rats. Hematologic data support red blood cell system toxicity and signs of anemia. Clinical chemistry and organ weight data indicate liver, kidney, and heart as target organs for test substance toxicity. Considering the multiplicity of treatment-related effects from a short treatment period of 7 days with dose levels as low as 30 mg/kg/day, the test substance toxic potential appears high.

f. Seven-Day Oral Toxicity Study with [redacted] in Rats

This study was designed to assess subacute toxicity and kinetics of the test substance given to rats for 7 days. Doses were corrected for test substance purity. In the subacute toxicity portion, 5 male and 5 female Crl:CD (SD) rats per group were given 0 (vehicle control), 30, 100, or 300 mg/kg/day of test substance in water by gavage daily for 7 days with terminal sacrifice on study day 8. Rats were 6 weeks old at the start of treatment. In the subacute toxicity portion, rats were evaluated for survival, clinical signs, body weight, hematology, clinical chemistry, gross pathology, histopathology, and organ weights.

All animals survived.

Clinical signs were unremarkable.

Body weight gain was normal.

In hematology, hemoglobin and hematocrit were decreased in males given 300 mg/kg/day and red blood cell counts were lower in females given 300 mg/kg/day,

In clinical chemistry, there were decreases in cholesterol and increases in alkaline phosphatase in all treated groups of males, decreases in globulin and triglycerides in males given 100 or 300 mg/kg/day, increases in biliary urea nitrogen and glucose and decreases in creatinine, total protein, and calcium in males given 300 mg/kg/day, and decreases in bilirubin in females given 300 mg/kg/day.

Absolute and relative (organ/body) liver weights were increased in all treated groups of males and in females given 300 mg/kg/day. Relative kidney weights were elevated in all treated groups of males, and absolute kidney weights were higher in males given 100 mg/kg/day.

Gross pathology was unremarkable.

In histopathology, minimal to mild hepatocellular hypertrophy in liver was found in all treated groups of males and females.

A NOAEL is not established based on changes in clinical chemistry and organ weights indicative of liver effects in all groups of treated male rats. Hematologic data in rats given 300 mg/kg/day support red blood cell system toxicity and signs of anemia. Clinical chemistry and organ weight data indicate liver and kidney as target organs for test substance toxicity. Considering the multiplicity of treatment-related effects from a short treatment period of 7 days with dose levels as low as 30 mg/kg/day, the test substance toxic potential appears high.

g. Seven-Day Oral Toxicity Study with [redacted] in Mice

This study was designed to assess subacute toxicity and kinetics of the test substance given to mice for 7 days. Doses were corrected for test substance purity. In the subacute toxicity portion, 5 male Crl:CD1 (ICR) mice per group were given 0 (vehicle control) or 30 mg/kg/day of test substance in water by gavage daily for 7 days with terminal sacrifice on study day 8. Mice were 6 weeks old at the start of treatment. In the subacute toxicity portion, rats were evaluated for survival, clinical signs, body weight, gross pathology, histopathology, and organ weights.

All animals survived.

Clinical signs were unremarkable.

Body weight gain was slightly higher in treated males.

Absolute and relative (organ/body) liver weights were increased in treated males.

Gross pathology was unremarkable.

In histopathology, minimal single cell necrosis of hepatocytes, moderate hepatocellular hypertrophy, and moderate increases in mitotic figures, all in liver, was found in treated males.

A NOAEL is not established based on signs of liver toxicity. Considering the treatment-related toxic signs in liver from a short treatment period of 7 days with a dose level as low as 30 mg/kg/day, the test substance toxic potential appears strong.

h. Seven-Day Oral Toxicity Study with [redacted] in Mice

This study was designed to assess subacute toxicity of the test substance given to mice for 7 days. Doses were corrected for test substance purity. In the subacute toxicity portion, 5 male Crl:CD1 (ICR) mice per group were given 0 (vehicle control) or 30 mg/kg/day of test substance in water by gavage daily for 7 days with terminal sacrifice on study day 8. Mice were 6 weeks old at the start of treatment. In the subacute toxicity portion, rats were evaluated for survival, clinical signs, body weight, gross pathology, histopathology, and organ weights.

All animals survived.

Clinical signs were unremarkable.

Body weight gain was slightly higher in treated males.

Absolute and relative (organ/body) liver weights were increased in treated males.

Gross pathology was unremarkable.

In histopathology, minimal single cell necrosis of hepatocytes, moderate hepatocellular hypertrophy, and moderate increases in mitotic figures, all in liver, was found in treated males.

A NOAEL is not established based on signs of liver toxicity. Considering the treatment-related toxic signs in liver from a short treatment period of 7 days with a dose level as low as 30 mg/kg/day, the test substance toxic potential appears strong. In both 7-day studies in mice described herein, the results were similar.

I. Acute Dermal Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 402. Onto intact skin shaved free of fur of each of 5 male and 5 female Crl:CD (SD) rats was applied 5,000 mg/kg of neat test material under semi-occlusive dressing. Exposure to test substance was 24 hours. Animals were observed for survival, clinical signs, body weight, and gross pathology through terminal sacrifice on study day 15. Irritation at test sites was scored by the Draize method.

All animals survived.

The acute dermal LD_{50} was above 5,000 mg/kg.

There were no signs of irritation at application sites in males (Draize score of 0). At application sites in females, there were well-defined erythema (maximum Draize score of 2) which disappeared by 2 days post-treatment, no evidence of edema, and hyperkeratosis and ulceration which cleared by day 13 after treatment. This study was not a skin irritation test per guideline, i.e., OECD guideline 404; however, by Draize scoring, the test substance was slightly irritating in females in this study

Clinical signs, gross pathology, and body weight were unremarkable.

Results of this study support low acute dermal toxicity by the test material.

j. Eye Irritation Study with [redacted] in Rabbits

This study is consistent with OECD guideline 405. Into one eye of 1 male New Zealand white rabbits was applied 0.1 ml of undiluted test material. Irritation was scored according to the Draize method and examined with fluorescein stain during 28 hours post-treatment.

Discoloration of the conjunctival membrane of the treated eye was interpreted as necrosis. Corneal opacity, iritis, and chemosis and discharge in conjunctivae were observed. Observed eye effects did not reverse, and the animal was killed at the end of the observation for humane reasons. The maximum Draize score was 61, in the criteria for "severely irritating", but the required observation period of 7 days was not done to see if the criteria for stronger severity would have been met.

The investigators concluded eye effects "...appeared to look like necrosis". Considering results of this study as signs of necrosis, a high concern for eye irritation by the test material is concluded..

k. Dermal Irritation Study with [redacted] in Rabbits

This study is consistent with OECD guideline 404. Onto intact skin clipped free of fur of each of 3 New Zealand white rabbits (sex not reported) was applied 0.5 ml of undiluted test material under semi-occlusive dressing. Exposure to test substance was 4 hours. Irritation was

scored according to the Draize method during 72 hours post-treatment.

Very slight to well-defined erythema observed on test sites of all rabbits cleared by 24 hours post-treatment. No signs of edema were found. The maximum mean Draize score was 1.9 at 60 minutes after treatment.

By Draize criteria, the test material was slightly irritating to skin only at the 60-minute observation time, which supports low concern for this effect.

l. Acute Oral Toxicity Study with [redacted] in Mice

This study is consistent with OECD guideline 425. Female Crl:CD (ICR) mice were given test substance suspended in deionized water by gavage at a dose of 175 (1 mouse), 550 (3 mice) , or 1,750 mg/kg (3 mice). Animals were observed for survival, clinical signs, body weight, and gross pathology through sacrifice on study day 14.

No deaths occurred in the 175 and 550 mg/kg groups. All females given 1,750 mg/kg died on the day of or the day after dosing.

The estimated acute oral LD_{50} was 1,030 mg/kg.

Clinical signs in decedents were lethargy and low posture. No clinical signs were observed in survivors.

Survivor body weight was normal.

Gross pathology was unremarkable.

The estimated acute oral LD_{50} of 1,030 mg/kg supports low acute oral toxicity in this study.

m. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 425. Female Crl:CD (SD) rats were given neat test substance by gavage at a dose of 175 (2 rats), 550 (4 rats) , or 1,750 mg/kg (3 rats). Animals were observed for survival, clinical signs, body weight, gross pathology, and histopathology of gross lesions, heart, liver, and kidneys through sacrifice on study day 14-17.

No deaths occurred in the 175 mg/kg group. Two females given 550 mg/kg died on study day 2 or study day 17 (killed *in extremis*), and all females given 1,750 mg/kg died on the day of or the day after dosing. Cause of death was diagnosed as acute gastritis.

The estimated acute oral LD_{50} was 550 mg/kg.

Clinical signs in rats given 1,750 mg/kg included oral discharge, closed eyes, lethargy, wet fur, high posture, and ataxia. Clinical signs in rats given 550 mg/kg included lung noise, oral discharge, no feces, high posture, wet and stained fur No clinical signs other than stained and wet fur were observed in rats given 175 mg/kg.

Survivor body weight was normal. One rat given 550 mg/kg and sacrificed *in extremis* on day 17 lost weight.

Gross pathology was unremarkable except for discoloration, increased thickness, and/or ulcers/erosions in stomach of decedents.

Histopathology was normal except for degenerative necrosis, erosion/ulcer, and edema in stomach of decedents and acute tubular necrosis in kidney of decedents..

The estimated acute oral LD_{50} of 550 mg/kg supports low acute oral toxicity in this study. Irritation toxicity in stomach, the site of direct exposure, and kidney toxicity were evident at doses above 175 mg/kg.

n. Acute Oral Toxicity Study with [redacted]t in Rats

This study is consistent with OECD guideline 425. Male Crl:CD (SD) rats were given neat test substance by gavage at a dose of 175 (1 rat), 550 (2 rats) , 1,750 (4 rats), or 5,000 mg/kg (3 rats). Animals were observed for survival, clinical signs, body weight, and gross pathology through sacrifice on study day 14.

No deaths occurred in the 175 and 550 mg/kg groups. One male given 1,750 mg/kg died on study day 2, and all males given 5,000 mg/kg died on study day 1 or 2.

The estimated acute oral LD_{50} was 1,750 mg/kg.

Clinical signs in survivors included lethargy, wet and stained fur, and low posture. Clinical signs in decedents included lethargy, lung noise, decreased muscle tone, and stained and wet fur.

Survivor body weight was normal.

Gross pathology was unremarkable except for stained skin, expanded lungs, eye discoloration, and stomach discoloration in decedents.

The estimated acute oral LD_{50} of 1,750 mg/kg supports low acute oral toxicity in this study.

o. Corrositex *In Vitro* Test with [redacted]

Corrositex is described as a standardized and quantitative *in vitro* corrosivity test. However, this test does not presently meet OPPTS and OECD guidelines for skin irritation testing. Basically, the ability of the presumed corrosive test substance to penetrate a collagen biomembrane, as determined by color change in a liquid chemical detection medium, is compared to positive and negative controls. The investigators concluded that since the test substance penetrated the barrier as did the positive control (sulfuric acid), the test substance should be considered corrosive, However, it took around 1 hour and 8 minutes for the test substance to penetrate, whereas the positive control penetrated in approximately 1 minute. If time of penetration is a determining factor in this test, the results supporting the test agent as corrosive seem weak. To assess the skin irritation potential of the test substance, testing per OECD guideline 404 is recommended.

p. Two-Week Inhalation Toxicity Study with Transformation Byproducts in Rats

This study was done to assess systemic inhalation toxicity and the presence of micronuclei in bone marrow. Micronuclei assessment is done in a separate OPPT/RAD review. Ten male Crl:CD BR rats per dose group were exposed by inhalation to target concentrations of 0 (air control), 5,000, 25,000, or 175,000 ppm [redacted] or to 25,000 ppm [redacted]. an analytical concentration (measured by gas chromatography) of 0 (air control), 750, or 2,199 ppm. 6 hours/day, 5 days/week for 2 weeks. Five rats/group were sacrificed at the end of exposure, and 5 rats/group were sacrificed at the end of a 2-week recovery period. Nominal concentrations were 0, 750, and 3,000 ppm. Exposure was whole-body. Temperature and humidity in the inhalation chamber apparently were satisfactory. During exposure, oxygen was added as needed to maintain an oxygen level of at least 19 %. Rats were 7 weeks old at the start of the study. Animals were observed for survival, clinical signs, body weight, hematology, clinical chemistry, urinalysis, organ weights, histopathology, and gross pathology.

All animals survived.

Body weight was normal.

Clinical signs were unremarkable except for reduced activity during exposure to 175,000 ppm with recovery after cessation of exposure.

Hematology, clinical chemistry, and urinalysis were normal.

Mean absolute brain weights were increased in animals exposed to 5,000, 25,000, or 175,000 ppm of [redacted]. However, relative (organ/body) brain weights were unaffected.

Mean absolute and relative liver weights were elevated in rats exposed to [redacted].

Gross pathology was unremarkable.

Except for hyaline droplets in kidney in animals exposed to 175,000 ppm, there were no treatment-related histopathologic findings.

A NOAEL of 175,000 ppm with [redacted] is concluded in this study. Hyaline droplets in kidney in animals exposed to 175,000 ppm are a sign of kidney nephropathy in male rats exposed to hydrocarbons which EPA has stated as irrelevant to humans. Increased absolute and relative liver weights preclude conclusion of 25,000 ppm as a NOAEL with [redacted].

Recognizing no female rats on study, only 1 exposure level of [redacted], and only 2 weeks of exposure, this study is patterned after OECD guideline 412.. Whole-body exposure is permissible per guideline. Since the exposure atmosphere was described as vapor, there apparently was no detectable test substance aerosol in the atmosphere at the high levels used.

q. Acute Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 423. Three female Crl:CD (SD) IGS BR rats were given 2,000 mg/kg and 6 female rats were given 300 mg/kg of test substance in distilled water. Dosing was by gavage. Animals were sacrificed on day 14 post-treatment and were observed for survival, clinical signs, body weight, and gross pathology.

No deaths occurred with 300 mg/kg. All animals given 2,000 mg/kg died within 1 day of treatment. The acute oral LD_{50} was between 300 and 2,000 mg/kg.

Clinical signs in decedents included hunched posture, lethargy, ataxia, decreased and noisy respiration, diuresis, and dehydration. Survivors showed no clinical signs. Body weight was normal in survivors.

Gross pathology was unremarkable in survivors. In decedents were found abnormally red lungs, dark liver, and dark kidneys.

Because 300 mg/kg, which did not cause death, is close to 500 mg/kg, which is the lowest dose in the OPPT criteria for low acute oral toxicity, and 2,000 mg/kg is well above 500 mg/kg, low acute oral toxicity is concluded to be supported in this study.

r. Twenty Eight-Day Oral Toxicity Study with [redacted] in Rats

This study is consistent with OECD guideline 407, and dose levels were based on a 14-day oral dose toxicity study. Five male and 5 female Crl:CD (SD) rats per group were given 0 (vehicle control), 5, 25, or 100 mg/kg/day of test substance in purified water by gavage daily for 28 days with terminal sacrifice on day 29. Additional groups of 5 males and 5 females per group were similarly treated with 0 (vehicle controls) or 100 mg/kg/day and sacrificed after 14 days of recovery. Rats were 5 weeks old at the start of the study. The rats were evaluated for survival, functional observational battery, motor activity, clinical signs, body weight, food consumption,

hematology, clinical chemistry, urinalysis, gross pathology, organ weights, and histopathology.

All animals survived.

In hematology, prothrombin time and reticulocytes were increased in males and females given 100 mg/kg/day, respectively.

In clinical chemistry, alanine aminotransferase (ALT) and albumin/globulin ratio were increased in males given 100 mg/kg/day, ALT was increased in treated recovery males, cholesterol was decreased in males given 100 mg/kg/day, and bilirubin was decreased in females given 100 mg/kg/day.

Absolute and relative (organ/body) kidney weights were increased in males given 25 or 100 mg/kg/day and in treated recovery females, absolute and relative liver weights were increased in males given 100 mg/kg/day, and relative adrenal weights were increased in males given 100 mg/kg/day.

In gross pathology, there were elevations of the limiting ridge of the forestomach in 4 males and 1 female given 100 mg/kg/day and enlarged liver in 2 males given 100 mg/kg/day.

In histopathology, there were squamous cell hyperplasia in the limiting ridge of the forestomach in both sexes given 100 mg/kg/day, diffuse hypertrophy of hepatocytes with granular-degeneration in liver of males given 100 mg/kg/day, focal necrosis of hepatocytes in liver in 1 female given 100 mg/kg/day, tubular cell epithelium hyperplasia in kidney in 1 female given 100 mg/kg/day, and a solitary cyst in kidney medulla in 1 male given 100 mg/kg/day.

Other findings were unremarkable.

Based on increases in absolute and relative kidney weights in males at higher dose levels, the investigators concluded a NOEL of 5 mg/kg/day. This conclusion is acceptable as a NOAEL. In clinical chemistry and pathology, signs of kidney, liver, and forestomach toxicity were found in animals given 100 mg/kg/day.